Electron Transport Pharmacology

Introduction

This lesson contains great, discrete board fodder topics, mostly useful when they are recognized as distractions. The medications here are either not used or cause something else that should cause them to be discussed in an alternative lesson topic. However, we're going to review the ETC, reveal the truth about electron flow, and note potential test tricks. In fact, in clinical practice Dr. Williams hasn't encountered some of these medications, despite their being quite prevalent in board review materials for Step 1.

Electron Transport Chain, Drugs, and Toxicity

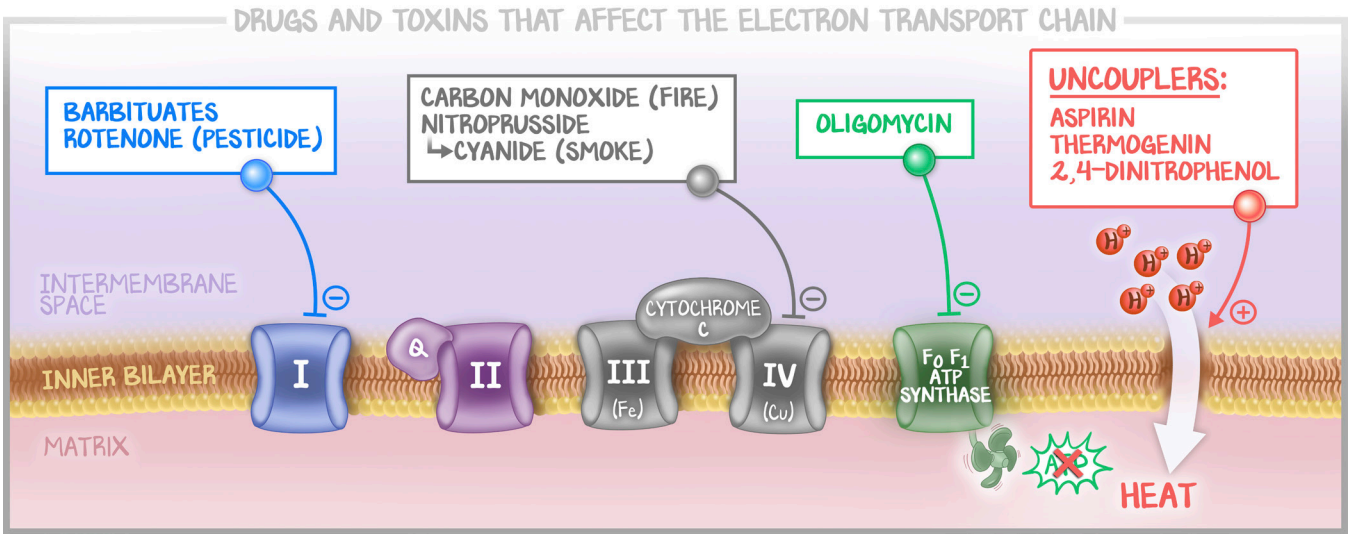

Figure 7.1: Drugs and Toxins That Affect the ETC
A color-coded map of which drugs affect which part of the electron transport chain.

Complex I: **Barbiturates** in lethal doses and the insecticide **rotenone** (this is not an organophosphate but is another pesticide, so be careful) **block complex I** (NADH dehydrogenase). This is why "the truth about the ETC" is important. Rotenone blocks the transfer of the electron energy from complex I to Q-complex II. That means that all the NADH are useless. But it also means that $FADH_2$ can still work. Which is why rotenone exposure "isn't as bad" as cyanide toxicity. Because rotenone is a **pesticide** and pesticides is a common way the test incorporates organophosphate poisoning, be sure not to confuse rotenone and organophosphates.

Complex IV: **Cyanide** toxicity **irreversibly binds complex IV** *(a/a3)*. That means that **oxygen cannot be oxidized**. That means it's as if the cell is without oxygen. This is bad. Cyanide is found in smoke, especially the burning of **polyurethane** (mattresses) and through a byproduct of the **anti-hypertensive infusion of nitroprusside**. One would think that with that as a possible side effect, we'd have stopped using nitroprusside. Well, we have. The boards, however, have not. Even though the only other way we'd be exposed to cyanide is a death-capsule from James Bond, nitroprusside can cause CN toxicity; **thiosulfate** is the **antidote**. That fact, the medication causing a deadly side effect with an antidote, is why it persists on the exam.

Carbon monoxide (CO) also binds to **complex IV** *(a/a3)*. Its binding is weaker than cyanide and is reversible. Carbon monoxide more commonly causes problem with **hemoglobin** than with the

electron transport chain. CO aggressively competes for oxygen-binding sites on hemoglobin, and CO has higher affinity for these binding sites, meaning that CO will displace oxygen from hemoglobin. Because CO binds to hemoglobin more tightly than oxygen, the oxygen-binding sites on hemoglobin are "fully saturated" and so the **oxygen saturation will be 100%** despite no oxygen being delivered to the cells. Also, the patient will appear flush, characterized by **cherry-red cheeks**. However, the CO on the hemoglobin (which can be detected with an arterial blood gas assessing for **methemoglobinemia**) doesn't deliver oxygen to tissues, and even though the RBCs go through the lungs, CO stays on the hemoglobin instead of oxygen. Carbon monoxide is common—**propane tanks**, **vehicle exhaust**, and **house fires** all expose patients to CO. Administer massive doses of oxygen (increasing the partial pressure of oxygen in the plasma has small benefit, but the more oxygen you administer, the more CO you can compete for on hemoglobin).

F_OF_1-ATP-Synthase: **Oligomycin**, a drug we hadn't heard of until we sat down to create this lecture, **plugs F_O**. Without harnessing the electrochemical gradient, there is no power, so all ATP synthesis stops. Because it's an antibiotic that ends in -mycin, you may be tempted to choose it on the exam in place of something else—such as the macrolides we'll study in the antibiotics that affect translation and transcription. Don't!

Uncouplers Are the Most Dangerous

The electrochemical gradient involves voltage and a concentration gradient. The flow of ions back across the inner mitochondrial membrane generates energy. The F_OF_1-ATP-synthase uses that energy to make ATP. Well, if **the H^+ gradient is uncoupled from the ATP-synthase**, allowing H^+ ions to flow back across the membrane anywhere but the F_OF_1-ATP-synthase, there are two problems. One, no ATP is made. Two, energy is still created, but it's not being used to make ATP. The energy of the H^+ coming across the mitochondrial membrane is released as **heat**. So not only is there **no ATP** to run the cells, there is also **malignant hyperthermia**.

2,4-Dinitrophenol was used as a weight-loss agent in ancient times. People died, because it uncoupled oxidative phosphorylation. Because history must not repeat itself, 2,4-di-nitro-phenol pops up occasionally on exams as a friendly reminder.

Thermogenin (heat-generating protein), now called **uncoupling protein** (UCP), is a **physiological uncoupling** in newborns. They are born with lots of adipose. A special variant is called **brown adipose**, brown fat. In order to ensure baby stays warm, brown adipose naturally uncouples oxidative phosphorylation a little bit. Brown fat is found near the kidneys, neck, chest, and scapulae. These areas heat up more than the rest of baby, effectively keeping the brain, lungs, heart, and kidney warm and functioning.

Aspirin (salicylic acid) in toxic doses can also uncouple the electron transport chain. In early aspirin toxicity there is hyperventilation and a respiratory alkalosis. The anti-prostaglandin effects see to this. As salicylate levels rise even higher, they **uncouple the electron transport chain**, increasing oxygen consumption without generating ATP (O_2 receives that electron, H^+ are pumped into the intermembrane space, but the H^+ don't come through the synthase). This effectively increases the oxygen demand of all cells while generating heat. The heat alone can be fatal. Every formerly healthy cell is simultaneously getting plenty of oxygen and glucose, and being starved for ATP. Eventually, the oxygen demands exceed delivery, and the cells are forced into **anaerobic metabolism**, leading to an elevation in lactic acid. The worst cases of salicylate toxicity present with **fever** (uncoupling energy loss),

lactic acidosis (the relative anaerobic environment), and **renal failure and encephalopathy** (the most metabolically active cells take the hit first).

Don't Be Tricked

It's a challenge to find a medication that uncouples the electron transport chain. And once it has been uncoupled, the medication has to wear off—there's nothing you can do about it.

Malignant hyperthermia caused by inhaled anesthetic gases such as **halothane**, is treated with **dantrolene**, which may also prevent febrility, confusion, and relative anaerobia. These patients would be easy to spot—having just received anesthesia (halothane) and not having breathed in burning mattresses or smoke from a burning house (CN, CO).

Organophosphate poisoning is caused by pesticides. Organophosphate poisoning is discussed in (General Pharmacology #9: *Cholinergics (PNS)*). It will cause salivation, lacrimation, urination, defecation, GI upset, and emesis, but not fever.

YOU MAY SEE THIS	AND GET TRICKED INTO THIS	WHEN REALLY IT'S THIS
Pesticides	Organophosphate poisoning, which has uncontrolled parasympathetics	Compromise of highly metabolic cells—brain, heart, kidneys
High fever related to medications	Malignant hyperthermia, which is from anesthetic gases like halothane, treated with dantrolene	Uncouplers, like aspirin, which also cause high fever, but aren't anesthetic gases
House fire	Cyanide toxicity, which is seen in healthcare as a medication side effect	Carbon monoxide poisoning, with altered mental status, cherry-red cheeks, and 100% sats
Antibiotic side-effect	Oligomycin	Any macrolide (azithromycin, clathromycin) or the related clindamycin

Table 7.1: Organophosphate vs. Rotenone
Don't be fooled by "pesticide." The presentations of organophosphate poisoning and rotenone poisoning are quite different.